Argonne NATIONAL LABORATORY

Argonne National Laboratory

Novel approach to studying cancer cells could reduce therapy side effects

ARGONNE, Ill. (May 5, 2006) — New cancer therapies with minimal side effects could result from a novel approach to studying cancer cells underway at the U.S. Department of Energy's Argonne National Laboratory. This research could also lead to new medications for diseases, such as eczema, macular degeneration and rheumatoid arthritis, which involve pathological capillary formation.

Argonne researchers are learning how healthy cells form capillaries by extending into tube-like shapes, a process called "angiogenesis." Tumors cells attract such capillaries and rely on them to provide oxygen for growth. Tumors often use those same capillaries to spread by sending out metastatic cells.

"We are focusing on endothelial cells, those cells which are the building blocks of blood vessels," said biologist and principal investigator Diane Rodi of Argonne's Biosciences Division.

"The idea," Rodi said, "is to identify which proteins endothelial cells produce when they reshape or morph into capillaries. Once we know those proteins, pharmaceutical companies may be able to develop drugs to starve tumors by disrupting protein function and stopping capillary growth."

Drugs that take this approach could be less toxic than most cancer therapies because they would target only those specific cells morphing into capillaries.

"By comparison," Rodi said, "most cancer drugs are anti-growth drugs that kill all the growing cells in the body. Most cancer therapies are not very specific, which is why they are so toxic."

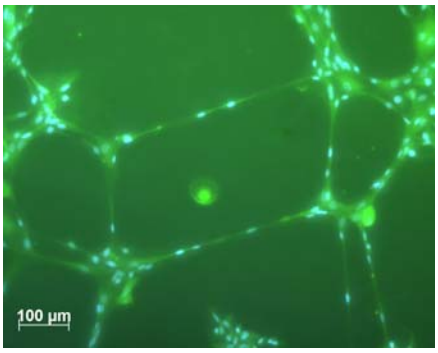
Pharmaceutical companies working specifically on stopping blood vessel formation "are focusing on disrupting the stimulation of cell growth, mainly by interfering with one particular growth factor called VEGF," Rodi said. "We decided to attack the problem from a different angle."

Rodi's research team has identified 217 genes associated specifically with capillary formation. The results were published in the April 15 issue of *Cancer Research*.

"This information will help with developing new drugs," Rodi said. "Once you know a gene product helps out in a process, then it automatically becomes a possible drug target."

Healthy adults usually only grow capillaries during wound healing and the menstrual cycle.

To identify genes associated only with capillary formation, Rodi's team grew and compared two cultures of endothelial cells. One culture was grown on plates that mimic tumor tissue and permit



DRUG TARGET – This immunofluorescent image of 8-hour-old endothelial cells illustrates capillary development.

PROTEIN RESEARCH – A researcher samples endothelial cells as they grow. This research found 217 proteins that are involved in capillary development. These proteins are targets for angiogenic drugs.

capillary formation. The second culture was grown on a plastic plate that does not permit capillary formation.

RNA samples were taken from both cultures at intervals of 30 minutes, 1 hour, 2 hours, 4 hours and 8 hours. RNA determines which proteins a cell produces.

“We wanted to find the proteins that are produced only when endothelial cells make a capillary,” she said. “We took all of the genes that were made on the tissue plate and subtracted those from the plastic plate. And we were left with 217.”

Each RNA sample was tested using microarray analysis at the University of Chicago. The microarrays hold 44,000 samples of known RNA coded by the human genome. A reaction on the microarray reveals which RNA is present.

Since the microarray studies only show that the potential for creating a certain protein exists, Argonne biologists needed to prove that the proteins were actually present. They looked for, and found, 16 of the morphogenesis-specific proteins in the capillaries at the 8-hour mark.

Human protein antibodies are necessary to prove that the 217 proteins are in the capillaries, but these antibodies are not easily found—only 50 are commercially available. Rodi’s team is working with another Argonne group that has developed a novel approach to express human proteins in bacteria. That group is growing more of the proteins to be used for antibody selection and testing for more of the 217 proteins in the capillaries.

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High-resolution versions of the images inthis document may be downloaded at www.anl.gov/Media_Center/News/2006/BIO060505.html

Research bonus

The capillary research revealed a bonus insight into a still mysterious aspect of cells—their polarity. Cells are not the same all over their surface—different sections perform different tasks, such as acting as environmental sensors or making little “feet” to mediate cell movement. But researchers do not yet know all the genes involved in polarity.

The majority of the 217 proteins identified by the Argonne group perform functions associated with polarity, such as movement within the cell, long distance migration, cytoskeletal reorganization and cellular stickiness. The Argonne study revealed that more angiogenic genes—those associated with the formation of new blood vessels—are involved in polarity than previously believed, and identified a large number of novel proteins that may control the rate of blood vessel formation.